D-MEM PhD-UNIMI | Doctorate program Milan EXPERIMENTAL MEDICINE

BIOMETRA

UNIVERSITÀ DEGLI STUDI DI MILANO

International PhD Program in Experimental Medicine

D-MEM SEMINAR

SAVERIO TEDESCO

UCL, THE FRANCIS CRICK INSTITUTE, LONDON

FEBRUARY 16, 2024 - 4 P.M.

Aula Magna, LITA

Engineering human skeletal muscle for advanced modelling of neuromuscular diseases and therapeutics

Skeletal muscle is a complex tissue composed of multinucleated myofibres supported by a variety of cell types and a specialised extracellular matrix (ECM), compromised in severe incurable neuromuscular diseases such as muscular dystrophies. Limitations in animal models and lack of reliable human(ised) in vitro models currently pose hurdles towards development of novel neuromuscular therapies. To address these limitations we developed three-dimensional (3D) human skeletal muscle constructs to model different morphological and functional defects in tissue compartments impaired in muscular dystrophies (e.g., sarcolemma, nuclear envelope, ECM). 3D muscles were developed from human myoblasts fibroblasts or induced pluripotent stem cells (iPSCs) differentiated into myogenic, neural and vascular progenitor cells, and then combined with biomaterials to generate aligned myofibre scaffolds containing ECM, vascular networks and motoneurons. Engineered muscles recapitulated molecular, morphological, and functional characteristics of human skeletal muscle, providing a high-fidelity platform to study muscle pathology, such as the emergence of nuclear abnormalities in muscular dystrophies caused by mutant nuclear lamins. To further validate this approach in another severe, congenital muscle disease with abnormal myonuclear features, we developed a new 3D model of X-linked centronuclear (myotubular) myopathy, identifying morphological and functional disease-associated readouts for therapeutic development. Moreover, we extended this technology to another incurable congenital muscular dystrophy characterised by abnormal ECM, detecting disease-associated readouts at macro- and micro-scopic scale.
Finally, this 3D platform and its disease-associated in vitro outcome measures were utilised to test both mutation-independent and -specific genetic therapies, laying the foundations for a multi-functional platform for precision medicine in neuromuscular diseases.